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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. No.	:	09/871,227
Applicant	:	Hector F. DeLuca et al
Filed	:	May 31, 2001
Title	:	2-Ethyl and 2-Ethylene-19-Nor-Vitamin D Compounds
TC/A.U.	:	1616
Examiner	:	Barbara P. Badio
Docket No.	:	1256-00765

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 22nd day of September, 2003.

Dorothy A. Hauser — September 22, 2003 Date

DECLARATION OF HECTOR F. DELUCA

Mail Stop:
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Hector F. DeLuca, hereby declare as follows:

1. That I am one of the named inventors in the above-identified patent application;

2. That I have read and I am familiar with the final rejection set forth in the Patent Office Action dated April 25, 2003;

3. That I have read and I am familiar with the two prior references cited and applied against the claims of the present application by the Patent Examiner, namely, DeLuca et al U.S. Patent 5,945,410, and DeLuca et al U.S. Patent 5,843,928;

4. That I have conducted and supervised a series of tests in order to determine, evaluate and compare the intestinal calcium transport activity and bone calcium mobilization activity of the following compounds:

1) 2α-Methyl-19-Nor-1,25$(OH)_2D_3$
2) 2β-Methyl-19-Nor-1,25$(OH)_2D_3$
3) 2α-Methyl-19-Nor-(20S)-1,25$(OH)_2D_3$
4) 2β-Methyl-19-Nor-(20S)-1,25$(OH)_2D_3$
5) 2-Methylene-19-Nor-1,25$(OH)_2D_3$
6) 2-Methylene-19-Nor-(20S)-1,25$(OH)_2D_3$
7) 2α-Ethyl-19-Nor-1,25$(OH)_2D_3$
8) 2β-Ethyl-19-Nor-1,25$(OH)_2D_3$
9) 2α-Ethyl-19-Nor-(20S)-1,25$(OH)_2D_3$
10) 2β-Ethyl-19-Nor-(20S)-1,25$(OH)_2D_3$
11) 2-Ethylidene-19-Nor-1,25$(OH)_2D_3$ (E-isomer)
12) 2-Ethylidene-19-Nor-1,25$(OH)_2D_3$ (Z-isomer)
13) 2-Ethylidene-19-Nor-(20S)-1,25$(OH)_2D_3$ (E-isomer)
14) 2-Ethylidene-19-Nor-(20S)-1,25$(OH)_2D_3$ (Z-isomer)

5. That the first six compounds listed above in paragraph 4 are prior art compounds found in the '410 and '928 references cited by the Examiner;

6. That the last eight compounds listed above in paragraph 4 are the compounds specifically disclosed in the patent application and claimed in claims 1-8 therein;

7. That the intestinal calcium transport activity and bone calcium mobilization activity of all these compounds were tested and the data obtained under identical conditions. More specifically, weanling male rats were maintained on a 0.47% calcium, 0.3% phosphorus vitamin D deficient diet for one week and then given the same diet except containing 0.02% calcium for a minimum of two weeks. During the last week

they were given the indicated dose of compound by intraperitoneal injection in 0.1ml of 95% propylene glycol and 5% ethanol each day for seven days. Controls received only the vehicle. Twenty-four hours after the last dose, the rats were sacrificed and intestinal calcium transport was determined by everted sac technique and serum calcium determined by atomic absorption spectrometry. There were at least five rats per group and the values obtained represent the mean ± SEM;

8. That the results of the tests are represented by the data set forth in Tables 1 and 2 in Exhibits A and B attached hereto;

9. That for convenience and to more clearly illustrate differences, the data is presented in a "Δ" format, i.e. the difference between the value recorded for that compound and the value recorded for vitamin D deficient control animals. Thus, the Δ value reported for control animals is "0" and the value reported for the remaining compounds tested show the difference between the values for that compound and control;

10. That due to the structural similarity between the prior art compounds and the presently claimed compounds, one would expect that a comparison of each claimed compound with its closest prior art compound would result in both compounds having equivalent biological activity; surprising however, the presently claimed compounds have biological activity which is dissimilar from its closest prior art compound, as shown and described as follows:

EXHIBIT A

2α-Methyl-19-Nor-1α,25-Dihydroxyvitamin D_3 Versus
2α-Ethyl-19-Nor-1α,25-Dihydroxyvitamin D_3

11. That the data in Exhibit A show that 2α-methyl-19-nor-1α,25-dihydroxyvitamin D_3 had relatively high intestinal calcium transport activity as well as relatively high bone calcium mobilization activity. In contrast, although the claimed

compound 2α-ethyl-19-nor-1α,25-dihydroxyvitamin D_3 also showed relatively high bone calcium mobilization activity, it showed little, if any, intestinal calcium transport activity; thus, the claimed compound is similar to the prior art compound in that it has relatively strong bone calcium mobilization activity, but is different from the prior art compound in that it has little, if any, intestinal calcium transport activity;

2β-Methyl-19-Nor-1α,25-Dihydroxyvitamin D_3 Versus
2β-Ethyl-19-Nor-1α,25-Dihydroxyvitamin D_3

12. That the data in Exhibit A show that the prior art 2β-methyl-19-nor-1α,25-dihydroxyvitamin D_3 compound showed little, if any, intestinal calcium transport activity and little, if any, bone calcium mobilization activity. In contrast, although the claimed 2β-ethyl-19-nor-1α,25-dihydroxyvitamin D_3 compound also showed little, if any, intestinal calcium transport activity, it showed relatively high bone calcium mobilization activity; thus, a comparison of the claimed compound with the closest prior art compound shows that although both compounds have little, if any, intestinal calcium transport activity, the presently claimed compound has significant bone calcium mobilization activity whereas the prior art compound has little, if any bone calcium mobilization activity;

2α-Methyl-19-Nor-(20S)-1α,25-Dihydroxyvitamin D_3 Versus
2α-Ethyl-19-Nor-(20S)-1α,25-Dihydroxyvitamin D_3

13. That the data in Exhibit A show that the prior art compound 1α-methyl-19-nor-(20S)-1α,25-dihydroxyvitamin D_3 has very strong intestinal calcium transport activity and also showed very strong bone calcium mobilization activity; in contrast, although the herein claimed compound 2α-ethyl-19-nor-(20S)-1α,25-dihydroxyvitamin D_3 produced a significant bone calcium mobilization response, it showed relatively weak intestinal calcium transport activity; thus the claimed compound is similar to the prior art

compound in that they both have significant bone calcium mobilization activity, but the claimed compound is different from the prior art compound in that the prior art compound also has very significant intestinal calcium transport activity whereas the claimed compound has relatively weak intestinal calcium transport activity;

2β-Methyl-19-Nor-(20S)-1α,25-Dihydroxyvitamin D_3 Versus
2β-Ethyl-19-Nor-(20S)-1α,25-Dihydroxyvitamin D_3

14. That the data in Table 1 show that 2β-methyl-19-nor-(20S)-1α,25-dihydroxyvitamin D_3 has some intestinal calcium transport activity, but is relatively weak in this regard, and has little, if any, bone calcium mobilization activity; in contrast, although the claimed 2β-ethyl-19-nor-(20S)-1α,25-dihydroxyvitamin D_3 compound also has relatively weak intestinal calcium transport activity, it has significant, and relatively strong, bone calcium mobilization activity; thus, the presently claimed compound is similar to the prior art compound in that it has very weak intestinal calcium transport activity, but is significantly different from the prior art compound in that it has relatively high bone calcium mobilization activity whereas the prior art compound has almost no bone calcium mobilization activity;

EXHIBIT B

2-Methylene-19-Nor-1α,25-Dihydroxyvitamin D_3 Versus
2-Ethylidene-19-Nor-1α,25-Dihydroxyvitamin D_3 (E and Z Isomers)

15. That the data in Table 2 show that 2-methylene-19-nor-1α,25-dihydroxyvitamin D_3 has little, if any, intestinal calcium transport activity, but has very strong bone calcium mobilization activity; in contrast, both the E and Z isomers of 2-ethylidene-19-nor-1α,25-dihydroxyvitamin D_3 had high intestinal calcium transport activity, but show little, if any, bone calcium mobilization activity; thus, the presently claimed E and Z isomers have activities which are basically the opposite of the closest

prior art compound, i.e. both compounds have relatively strong intestinal calcium transport activity, but little, if any bone calcium mobilization activity whereas the prior art compound has relatively high bone calcium mobilization activity and little, if any, intestinal calcium transport activity;

2-Methylene-19-Nor-(20S)-1α,25-Dihydroxyvitamin D_3 Versus
2-Ethylidene-19-Nor-(20S)-1α,25-Dihydroxyvitamin D_3 (E and Z Isomers)

16. The data in Table 2 show that the prior art compound 2-methylene-19-nor-(20S)-1α,25-dihydroxyvitamin D_3 has extremely high bone calcium mobilization activity, but little, if any, intestinal calcium transport activity; in contrast, although the E isomer of 2-ethylidene-19-nor-(20S)-1α,25-dihydroxyvitamin D_3 also showed very strong bone calcium mobilization activity, it also showed significant intestinal calcium transport activity; also, the Z isomer of 2-ethylidene-19-nor-(20S)-1α,25-dihydroxyvitamin D_3 showed little, if any, bone calcium mobilization activity and little, if any, intestinal calcium transport activity; thus, the two claimed E and Z isomers differ significantly from the closest prior art compound, i.e. the (20S) E isomer has significant intestinal calcium transport activity whereas the prior art compound does not, and the (20S) Z isomer has little, if any, bone calcium mobilization activity whereas the prior art compound has very strong bone calcium mobilization activity;

17. That as discussed herein and as shown in Exhibits A and B each of the claimed compounds, when compared to its closest prior art compound under identical conditions, has biological activities which are different from the closest prior art compound even though the claimed compounds are structurally similar and thus would be expected to have similar activities.

Declaration of Hector F. DeLuca
Application No. 09/871,227
Declaration Dated: September 22, 2003

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statement were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 9/08/03 By: Hector F. DeLuca

Attorneys for Applicant:

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Milwaukee, Wisconsin 53202
Attorney Docket No.: 1256-00765

EXHIBIT A

TABLE 1

Compound	Dose (pmol/day/ 7 days)	Δ Intestinal Calcium Transport (S/M)	Δ Serum Calcium (mg/100ml)
None (-D control)	Vehicle	0	0
2α-Methyl-19-Nor-1,25$(OH)_2D_3$	260	3.0 ± 0.5	1.9 ± 0.3
2α-Ethyl-19-Nor-1,25$(OH)_2D_3$	260	0.2 ± 0.0	1.2 ± 0.0
2β-Methyl-19-Nor-1,25$(OH)_2D_3$	260	0.8 ± 0.1	0.1 ± 0.0
2β-Ethyl-19-Nor-1,25$(OH)_2D_3$	260	0.1 ± 0.1	1.1 ± 0.0
2α-Methyl-19-Nor-(20S)-1,25$(OH)_2D_3$	260	5.5 ± 0.9	6.1 ± 0.01
2α-Ethyl-19-Nor-(20S)-1,25$(OH)_2D_3$	260	1.2 ± 0.0	3.1 ± 0.0
2β-Methyl-19-Nor-(20S)-1,25$(OH)_2D_3$	260	0.9 ± 0.1	0.2 ± 0.0
2β-Ethyl-19-Nor-(20S)-1,25$(OH)_2D_3$	260	0.3 ± 0.1	1.7 ± 0.0

EXHIBIT B

TABLE 2

Compound	Dose (pmol/day/7days)	Δ Intestinal Calcium Transport (S/M)	Δ Serum Calcium (mg/100ml)
None (-D Control)	Vehicle	0	0
2-Methylene-19-Nor-1,25$(OH)_2D_3$	130	0.2 ± 0.2	4.8 ± 0.04
2-Ethylidene-19-Nor-1,25$(OH)_2D_3$ (E-isomer)	130	3.8 ± 0.3	0.9 ± 0.1
2-Ethylidene-19-Nor-1,25$(OH)_2D_3$ (Z-isomer)	130	2.7 ± 0.2	0.1 ± 0.1
2-Methylene-19-Nor-(20S)-1,25$(OH)_2D_3$	130	0.2 ± 0.6	8.7 ± 0.34
2-Ethylidene-19-Nor-(20S)-1,25$(OH)_2D_3$ (E-isomer)	130	1.4 ± 0.6	8.0 ± 0.4
2-Ethylidene-19-Nor-(20S)-1,25$(OH)_2D_3$ (Z-isomer)	130	0.6 ± 0.1	0.1 ± 0.1